

#### § 113.4

Animal and Plant Health Inspection Service upon request.

(Approved by the Office of Management and Budget under control number 0579-0013)

[38 FR 29886, Oct. 30, 1973, as amended at 40 FR 758, Jan. 3, 1975; 40 FR 49768, Oct. 24, 1975; 41 FR 56627, Dec. 29, 1976; 48 FR 9506, Mar. 7, 1983; 48 FR 57473, Dec. 30, 1983; 50 FR 21799, May 29, 1985; 56 FR 66784, Dec. 26, 1991; 60 FR 14356, Mar. 17, 1995]

#### § 113.4 Exemptions to tests.

(a) The test methods and procedures contained in all applicable Standard Requirements shall be complied with unless otherwise exempted by the Administrator and provided that such exemption is noted in the filed Outline of Production for the product.

(b) Test methods and procedures by which the biological products shall be evaluated shall be designated in the Outline of Production for such products.

[38 FR 29887, Oct. 30, 1973, as amended at 56 FR 66784, Dec. 26, 1991]

#### § 113.5 General testing.

(a) No biological product shall be released prior to the completion of tests prescribed in a filed Outline of Production or Standard Requirements for the product to establish the product to be pure, safe, potent, and efficacious.

(b) Tests of biological products shall be observed by a competent employee of the manufacturer during all critical periods. A critical period shall be the time when certain specified reactions must occur in required tests to properly evaluate the results.

(c) Records of all tests shall be kept in accordance with part 116 of this chapter. Results of all required tests prescribed in the filed Outline of Production or the Standard Requirements for the product shall be submitted to Animal and Plant Health Inspection Service. Blank forms shall be furnished upon request to Animal and Plant Health Inspection Service.

(d) When the initial or any subsequent test is declared a "No test," the reasons shall be reported in the test records, the results shall not be considered as final, and the test may be repeated.

(e) When new test methods are developed and approved by Animal and

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Plant Health Inspection Service, biological products tested thereafter shall be evaluated by such methods, and if not found to be satisfactory when so tested shall not be released.

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[34 FR 18004, Nov. 4, 1969, as amended at 39 FR 25463, July 11, 1974; 40 FR 45420, Oct. 2, 1975; 40 FR 46093, Oct. 6, 1975; 41 FR 6751, Feb. 13, 1976; 48 FR 57473, Dec. 30, 1983; 56 FR 66784, Dec. 26, 1991]

#### § 113.6 Animal and Plant Health Inspection Service testing.

A biological product shall with reasonable certainty yield the results intended when used as recommended or suggested in its labeling or proposed labeling prior to the expiration date.

(a) The Administrator is authorized to cause a biological product, manufactured in the United States or imported into the United States, to be examined and tested for purity, safety, potency, or efficacy; in which case, the licensee or permittee shall withhold such product from the market until a determination has been made.

(b) The final results of each test conducted by the licensee and Animal and Plant Health Inspection Service shall be considered in evaluating a biological product. A serial or subserial which has been found unsatisfactory by a required test prescribed in a filed Outline of Production or Standard Requirement is not in compliance with the regulations and shall not be released for market.

[34 FR 18004, Nov. 7, 1969, as amended at 40 FR 45420, Oct. 2, 1975; 40 FR 53378, Nov. 18, 1975; 41 FR 6751, Feb. 13, 1976; 56 FR 66784, Dec. 26, 1991]

#### § 113.7 Multiple fractions.

(a) When a biological product contains more than one immunogenic fraction, the completed product shall be evaluated by tests applicable to each fraction.

(b) When similar potency tests are required for more than one fraction of a combination biological product, different animals must be used to evaluate each fraction except when written Standard Requirements or outlines of production make provisions and set

forth conditions for use of the same animals for testing different fractions.

(c) When the same safety test is required for more than one fraction, requirements are fulfilled by satisfactory results from one test of the completed product.

(d) When an inactivated fraction(s) is used as a diluent for a live virus fraction(s), the inactivated fraction(s) may be tested separately and the live virus fraction(s) may be tested separately: *Provided*, That, the viricidal test requirements prescribed in §113.100 are complied with.

(e) Virus titrations for a multivirus product shall be conducted by methods which will quantitate each virus.

[34 FR 18004, Nov. 7, 1969, as amended at 40 FR 46093, Oct. 6, 1975; 56 FR 66785, Dec. 26, 1991]

**§ 113.8 In vitro tests in lieu of animal tests for immunogenicity.**

(a) Master Seed which has been established as pure, safe, and immunogenic shall be used for preparing seed for production when specified in the Standard Requirements or in a filed Outline of Production. The Administrator may exempt a product from a required animal test for release when an evaluation can with reasonable certainty be made by:

(1) Subjecting the Master Seed to the applicable requirements prescribed in § 113.300 or § 113.64;

(2) Testing the Master Seed for immunogenicity in a manner acceptable to Animal and Plant Health Inspection Service;

(3) Establishing a satisfactory count or titer based on a predetermined protective dose plus an adequate overage allowance for adverse conditions and test error; and

(4) Conducting counts or titrations on each serial and subserial in an accepted test system.

(b) Each serial and subserial derived from an approved Master Seed shall be evaluated by a test procedure acceptable to Animal and Plant Health Inspection Service and either released to the firm for marketing or withheld from the market on the basis of the results of the test when compared with the required minimum. The evaluation

of such products shall be made in accordance with this paragraph.

(1) If the initial test shows the count or titer to equal or exceed the required minimum, the serial or subserial is satisfactory without additional testing.

(2) If the initial test shows the count or titer to be lower than the required minimum, the serial or subserial may be retested, using double the number of samples. The average counts or titers obtained in the retests shall be determined. If the average is less than the required minimum, the serial or subserial is unsatisfactory without further consideration.

(3) If the average is equal to or greater than the required minimum, the following shall apply to live virus vaccines:

(i) If the difference between the average titer obtained in the retests and the titer obtained in the initial test is  $10^{0.7}$  or greater, the initial titer may be considered a result of test system error and the serial or subserial considered satisfactory for virus titer.

(ii) If the difference between the average titer obtained in the retests and the titer obtained in the initial test is less than  $10^{0.7}$ , a new average shall be determined using the titers obtained in all tests. If the new average is below the required minimum, the serial or subserial is unsatisfactory.

(4) If the average is equal to or greater than the required minimum, the following shall apply to bacterial vaccines:

(i) If the average count obtained in the retests is at least three times the count obtained in the initial test, the initial count may be considered a result of test system error and the serial or subserial considered satisfactory for bacterial count.

(ii) If the average count obtained in the retests is less than three times the count obtained in the initial test, a new average shall be determined using the counts obtained in all tests. If the new average count is below the required minimum, the serial or subserial is unsatisfactory.

(5) *Exceptions.* When a product is evaluated in terms other than  $\log_{10}$  virus titer values or organism count, a range shall be established to substitute for use in paragraphs (b)(3) or (4) of this